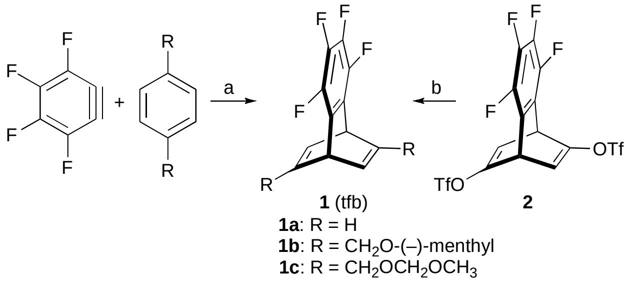
The concise synthesis of chiral tfb ligands and their application to rhodium-catalyzed asymmetric arylation of aldehydes

Takahiro Nishimura,* Hana Kumamoto, Makoto Nagaosa, and Tamio Hayashi*

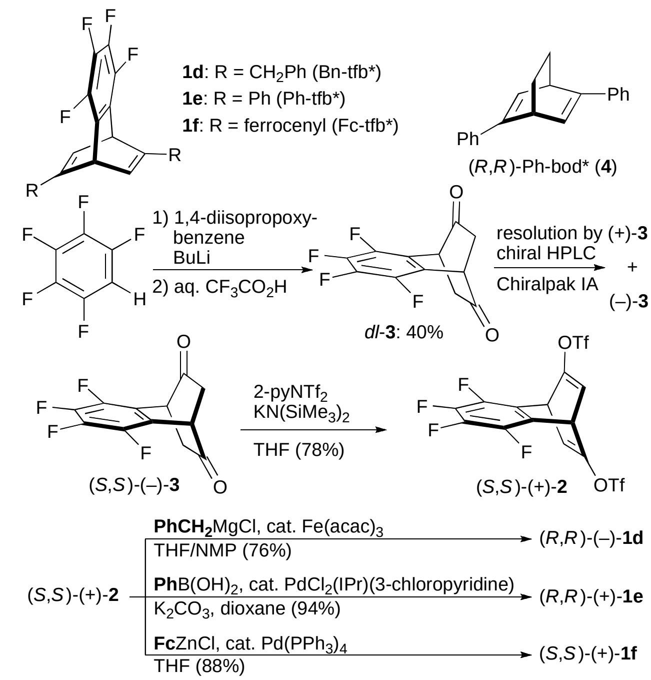
***C*$_2$-Symmetric tetrafluorobenzobarrelene ligands were prepared through the transition metal-catalyzed cross-coupling of an enantiopure tetrafluorobenzobicyclo[2.2.2]octatriene-2,5-diyl bis(trifluoro-methanesulfonate) with organometallic reagents. The diene ligands realized the rhodium-catalyzed asymmetric addition of arylboronic acids to aromatic aldehydes.**

Chiral dienes have been recently developed as a new class of chiral ligands for the transition metals, realizing highly efficient and enantioselective reactions.[1] Of the diene ligands bearing diverse bicyclic skeletons, tetrafluorobenzobicyclo-[2.2.2]octatriene (tetrafluorobenzobarrelene; tfb) **1a** and its derivatives[2] are attractive compounds because of their high coordination ability toward transition metals due to the small bite angle and electron-deficient characters.[3] In addition, the synthesis of the tfb dienes is easy; i.e. tfb **1a** is prepared in one step by the formal [4 + 2] cycloaddition of benzene with tetrafluorobenzyne generated from pentafluorophenyllithium or -magnesium (Scheme 1, route a).[2] The use of 1,4-disubstituted benzenes provides chiral tfb dienes. Recently, we reported the synthesis of enantiomerically pure disubstituted tfb dienes (**1b** and **1c**) via cycloaddition of tetrafluorobenzyne with the 1,4-disubstituted benzenes and their application to the rhodium- and iridium-catalyzed asymmetric addition of arylboronic acids.[4] One drawback of the direct preparation of chiral tfb dienes is the difficulty of the synthesis of tfb **1** substituted with aromatic groups. Provided that the enantiopure ditriflate **2** is obtained, it is possible to prepare diverse chiral tfb dienes by transition metal-catalyzed cross-coupling reactions (route b). Here we report the development of *C*$_2$-symmetric disubstituted tetrafluorobenzobicyclo[2.2.2]octatrienes **1** and their successful application to the rhodium-catalyzed asymmetric arylation of aldehydes with arylboronic acids.

Chiral ditriflate **2** and tfb ligands **1d**–**f** were prepared through the straightforward pathways (Scheme 2). The [4 + 2] cycloaddition of 1,4-diisopropoxybenzene with tetrafluorobenzyne followed by hydrolysis gave *dl*-**3** in 40% yield.[5] The resolution of diketone *dl*-**3** by use of a chiral stationary phase column (Chiralpak IA)[6] gave both enantiomers (+)-**3** and (–)-**3**, which were transformed into ditriflate **2**.[7] Enantiopure ditriflate **2** was subjected to the cross-coupling reactions with benzylmagnesium chloride,[8] phenylboronic acid,[9] and ferrocenylzinc chloride[10] leading to **1d**, **1e**, and **1f**, respectively, in good yields. The reaction of chiral dienes **1d**–**f** with $[RhCl(C_2H_4)_2]_2$ gave rhodium complexes [RhCl(**1**)]$_2$ in high yields (Scheme 3). The absolute configuration of (*S*,*S*)-**1f** was assigned by the X-ray crystallographic analysis of its rhodium complex Rh(**1f**)[(η^6-C_6H_5)BPh_3] (Scheme 3, Figure 1).[11]

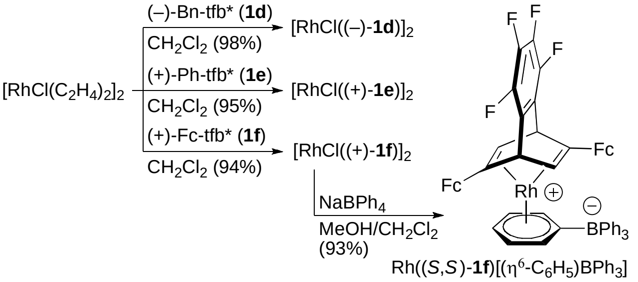


Scheme 1 Tetrafluorobenzobarrelenes (tfb).



Scheme 2 Synthesis of *C*$_2$-symmetric tetrafluorobenzobarrelenes (tfb*).

Asymmetric synthesis of diarylmethanols by the enantioselective arylation of aldehydes remains to be a very important objective in organic synthesis.[12] A successful development has been achieved in the asymmetric addition of arylzinc reagents to aldehydes by use of chiral ligands.[13] The transition metal-catalyzed asymmetric addition of organometallic reagents to aldehydes is another useful method for the synthesis of chiral diarylmethanols, where arylboronic acids are used as attractive arylating reagents. Since the first



Scheme 3 Synthesis of rhodium complexes.

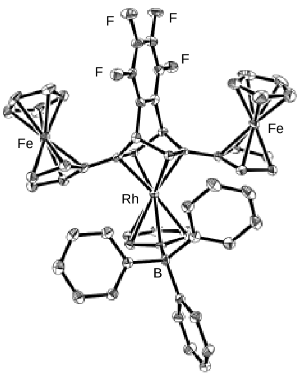
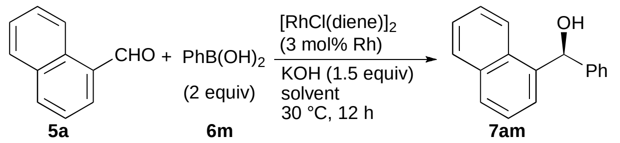


Fig. 1 ORTEP illustration of Rh((*S*,*S*)-**1f**)[(η^6-C_6H_5)BPh_3] with thermal ellipsoids drawn at 50% probability level. The solvent molecule (CH_2Cl_2) and hydrogens are omitted for clarity.

report of the rhodium-catalyzed asymmetric arylation of aldehydes by Miyaura in 1998,[14a] Rh,[1k, 14] Ni,[15] and Ru-catalyzed[16] reactions have been developed.

The new rhodium complexes having tfb ligands **1d**–**1f** were tested for the asymmetric arylation of aldehydes with arylboronic acids. The ligands **1b**, **1c**, and Ph-bod (**4**)[1c,d] were also used for comparison. Treatment of 1-naphthaldehyde (**5a**) with phenylboronic acid (**6m**) in the presence of [RhCl(**1b**)]$_2$ (3 mol% of Rh) and KOH (1.5 equiv) in dioxane/H_2O (4/1) at 30 °C for 12 h gave diarylmethanol **7am** in low yield and ee (25%, 16% ee) (Table 1, entry1). The yields of **7am** were also low in the reaction by use of the tfb ligands (**1c** and **1d**) substituted with alkyl groups (entries 2 and 3). On the other hand, Ph-tfb*(**1e**) displayed higher catalytic activity and enantioselectivity giving **7am** in 94% yield with 49% ee (entry 4). The same yield and enantioselectivity were observed in the reaction by use of Ph-bod* (**4**), which has phenyl groups on a bicyclo[2.2.2]octadiene skeleton (entry 5). These results imply that the electron-deficient character of the diene part substituted with the phenyl group improves the catalytic activity. Higher enantioselectivity was obtained with tfb ligand **1f** (Fc-tfb*) substituted with ferrocenyl groups, where the ee of **7am** was 72% (entry 6). The reaction solvents had a significant influence on the enantioselectivity. Thus, the reaction in protic solvents improved the ee of **7am** (entries 7–9), and the highest enantioselectivity (86% ee) was observed in *tert*-butyl alcohol (entry 9). The reaction with the catalyst loading of 1 mol% of rhodium proved to be completed within 3 h (entry 10). The absolute configuration of **7am** produced by use of (*S*,*S*)-**1f** was determined to be (*S*) by comparison of its specific rotation and the retention time of the chiral HPLC analysis with those reported previously.[14]

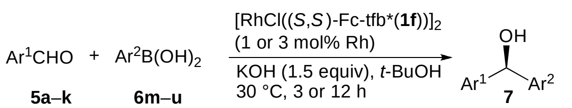
Table 1 Asymmetric addition of phenylboronic acid (**6m**) to 1-naphthaldehyde (**5a**)[a]



Entry	Ligand	Solvent	Yield (%)[b]	Ee (%)[c]
1	**1b**	1,4-dioxane/H_2O (4/1)	25[d]	16 (*S*)
2	**1c**	1,4-dioxane/H_2O (4/1)	30[d]	43 (*S*)
3	**1d**	1,4-dioxane/H_2O (4/1)	49[d]	27 (*S*)
4	**1e**	1,4-dioxane/H_2O (4/1)	94	49 (*S*)
5	**4**	1,4-dioxane/H_2O (4/1)	94	49 (*S*)
6	**1f**	1,4-dioxane/H_2O (4/1)	94	72 (*S*)
7	**1f**	methanol	99	78 (*S*)
8	**1f**	2-propanol	99	84 (*S*)
9	**1f**	*tert*-butyl alcohol	94	86 (*S*)
10[e]	**1f**	*tert*-butyl alcohol	95	86 (*S*)

[a] Reaction conditions; [RhCl(diene)]$_2$ (3.75 μmol, 3 mol% of Rh), **5a** (0.25 mmol), **6m** (0.50 mmol), KOH (0.38 mmol), solvent (1.0 mL), at 30 °C for 12 h. [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase column: Chiralcel OD-H. [d] Unreacted **5a** was observed. [e] Performed with [RhCl((*S*,*S*)-**1f**)]$_2$ (1 mol% of Rh) for 3 h.

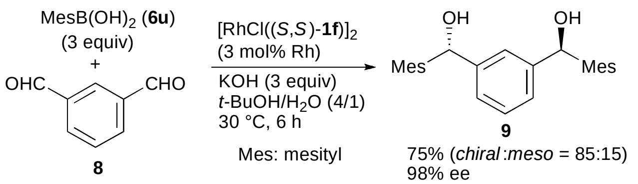
Table 2 Asymmetric addition of arylboronic acids (**6**) to aromatic aldehydes **5**[a]



Entry	Ar^1	Ar^2	Yield[b]	Ee[c]
1	1-Naphthyl (**5a**)	Ph (**6m**)	95 (**7am**)	86 (*S*)
2	2-ClC_6H_4 (**5b**)	Ph (**6m**)	97 (**7bm**)	84 (*S*)
3	2-BrC_6H_4 (**5c**)	Ph (**6m**)	95 (**7cm**)	84 (*S*)
4	2-$MeOC_6H_4$ (**5d**)	Ph (**6m**)	99 (**7dm**)	85 (*S*)
5	2-MeC_6H_4 (**5e**)	Ph (**6m**)	98 (**7em**)	86 (*S*)
6	3-MeC_6H_4 (**5f**)	Ph (**6m**)	96 (**7fm**)	80 (*S*)
7	4-MeC_6H_4 (**5g**)	Ph (**6m**)	99 (**7gm**)	78 (*S*)
8	4-BrC_6H_4 (**5h**)	Ph (**6m**)	85 (**7hm**)	78 (*S*)
9	2-Naphthyl (**5i**)	Ph (**6m**)	93 (**7im**)	82 (*S*)
10	3,4-(OC_2H_4O)C_6H_3 (**5j**)	Ph (**6m**)	94 (**7jm**)	79 (*S*)
11	Ferrocenyl (**5k**)	Ph (**6m**)	94 (**7km**)	85 (*S*)
12	1-Naphthyl (**5a**)	3,5-$Me_2C_6H_3$ (**6n**)	90 (**7an**)	87 (*S*)[d]
13[e]	1-Naphthyl (**5a**)	4-MeC_6H_4 (**6o**)	90 (**7ao**)	85 (*S*)
14	1-Naphthyl (**5a**)	3-MeC_6H_4 (**6p**)	93 (**7ap**)	87 (*S*)[d]
15[e]	1-Naphthyl (**5a**)	2-MeC_6H_4 (**6q**)	87 (**7aq**)	91 (*S*)
16[e]	1-Naphthyl (**5a**)	2-ClC_6H_4 (**6r**)	91 (**7ar**)	86 (*R*)[d]
17[e]	1-Naphthyl (**5a**)	2-MeO-5-MeC_6H_3 (**6s**)	97 (**7as**)	85 (*R*)[d]
18[e]	1-Naphthyl (**5a**)	2,6-$(MeO)_2C_6H_3$ (**6t**)	80 (**7at**)	84 (*R*)[d]
19[e]	1-Naphthyl (**5a**)	Mesityl (**6u**)	87 (**7au**)	94 (*R*)
20[e]	2-ClC_6H_4 (**5b**)	Mesityl (**6u**)	70 (**7bu**)	94 (*S*)[d]
21[e]	2-MeC_6H_4 (**5e**)	Mesityl (**6u**)	87 (**7eu**)	93 (*R*)[d]
22[e]	2-BrC_6H_4 (**5c**)	2-MeC_6H_4 (**6q**)	87 (**7cq**)	86 (*S*)[d]
23[e]	Ferrocenyl (**5k**)	Mesityl (**6u**)	85 (**7ku**)	84 (*S*)[d]
24[e]	Ferrocenyl (**5k**)	2-MeC_6H_4 (**6q**)	98 (**7kq**)	86 (*S*)

[a] Reaction conditions; [RhCl((*S*,*S*)-**1f**)]$_2$ (1 mol% of Rh), Ar^1CHO (0.25 mmol), $Ar^2B(OH)_2$ (0.50 mmol), KOH (0.38 mmol), *t*-BuOH (1.0 mL), at 30 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration was assigned by analogy with entry 1. [e] Performed with [RhCl((*S*,*S*)-**1f**)]$_2$ (3 mol% of Rh) for 12 h.

Table 2 summarizes the results obtained for the reactions of several aldehydes **5** with arylboronic acids **6**, which were carried out in the presence of [RhCl((*S*,*S*)-Fc-tfb*(**1f**))]$_2$ (1 or 3 mol% of Rh). The scope of aldehydes is broad, both substituted with electron-withdrawing groups and with electron-donating groups being good substrates to produce diarylmethanols in high yields (entries 1–11). The enantioselectivities in the phenylation of aldehydes having *ortho*-substituents (entries 1–5) on the benzene ring were higher than those obtained with *meta*- or *para*-substituted aromatic aldehydes (entries 6–9). The scope of arylboronic acids is also broad (entries 12–24), where the use of *ortho*-substituted arylboronic acids displayed higher enantioselectivities of diarylmethanols **7** (entries 13–15 for $MeC_6H_4B(OH)_2$). Thus, the present catalytic system is effective for the asymmetric synthesis of diarylmethanols having *ortho*-substituents on both aromatic rings, the enantioselectivity ranging between 84% and 94% ee (entries 15–22). The asymmetric double arylation of isophthalaldehyde (**8**) was also successful using mesitylboronic acid (**6u**) to give 98% ee of diol *chiral*-**9** (75% yield, *chiral*/*meso* = 85/15) (Scheme 4).[17]



Scheme 4 Asymmetric double arylation of isophthalaldehyde (**8**).

This work was supported by a Grant-in-Aid for Scientific Research (S) (19105002) from the MEXT, Japan.

Notes and references

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan. Fax: +81 75 753 3983; Tel: +81 75 753 3988; E-mail: tnishi@kuchem.kyoto-u.ac.jp; thayashi@kuchem.kyoto-u.ac.jp

1 For a review of chiral diene ligands, see: (*a*) C. Defieber, H. Grützmacher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4482. For selected examples of the asymmetric reactions using chiral diene ligands, see: (*b*) T. Hayashi, K. Ueyama, N. Tokunaga and K. Yoshida, *J. Am. Chem. Soc.*, 2003, **125**, 11508. (*c*) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13584. (*d*) Y. Otomaru, K. Okamoto, R. Shintani and T. Hayashi, *J. Org. Chem.*, 2005, **70**, 2503. (*e*) K. Okamoto, T. Hayashi and V. H. Rawal, *Org. Lett.*, 2008, **10**, 4387. (*f*) C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628. (*g*) J.-F. Paquin, C. Defieber, C. R. J. Stephenson and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 10850. (*h*) F. Läng, F. Breher, D. Stein and H. Grützmacher, *Organometallics*, 2005, **24**, 2997. (*i*) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro and W. Frey, *Adv. Synth. Catal.*, 2007, **349**, 2331. (*j*) Z.-Q. Wang, C.-G. Feng, M.-H. Xu and G.-Q. Lin, *J. Am. Chem. Soc.*, 2007, **129**, 5336. (*k*) T. Noël, K. Vandyck and J. Van der Eycken, *Tetrahedron*, 2007, **63**, 12961. (*l*) T. Gendrineau, O. Chuzel, H. Eijsberg, J.-P. Genet and S. Darses, *Angew. Chem., Int. Ed.*, 2008, **47**, 7669.

2 (*a*) J. P. N. Brewer and H. Heaney, *Tetrahedron Lett.*, 1965, **6**, 4709. (*b*) J. P. N. Brewer, I. F. Eckhard, H. Heaney and B. A. Marples, *J. Chem. Soc. C*, 1968, 664. (*c*) D. D. Callander, P. L. Coe, J. C. Tatlow and A. J. Uff, *Tetrahedron*, 1969, **25**, 25.

3 For a review, see: (*a*) M. A. Esteruelas and L. A. Oro, *Coord. Chem. Rev.*, 1999, **193–195**, 557. For selected examples, see: (*b*) D. M. Roe and A. G. Massey, *J. Organomet. Chem.*, 1969, **17**, 429. (*c*) D. M. Roe and A. G. Massey, *J. Organomet. Chem.*, 1971, **28**, 273. (*d*) R. Usón, L. A. Oro, R. Sariego, M. Valderrama and C. Rebullida, *J. Organomet. Chem.*, 1980, **197**, 87. (*e*) R. Usón, L. A. Oro, L. D. Carmona, M. A. Esteruelas, C. Foces-Foces, F. H. Cano, S. Garcia-Blanco, *J. Organomet. Chem.*, 1983, **254**, 249.

4 (*a*) T. Nishimura, M. Nagaosa and T. Hayashi, *Chem. Lett.*, 2008, **37**, 860. (*b*) T. Nishimura, Y. Yasuhara, M. Nagaosa and T. Hayashi, *Tetrahedron: Asymmetry*, 2008, **19**, 1778.

5 Compound **3** was prepared by a modified procedure. (*a*) B. Hankinson and H. Heaney, *Tetrahedron Lett.*, 1970, **16**, 1335. (*b*) P. C. Buxton, N. J. Hales, B. Hankinson, H. Heaney, S. V. Ley and R. P. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2681.

6 A semi-preparative column (2.0 cm I.D. × 25 cm) was used for the resolution of *dl*-**3**. See Electronic Supplementary Information.

7 K. Vandyck, B. Matthys, M. Willen, K. Robeyns, L. Van Meervelt and J. Van der Eycken, *Org. Lett.*, 2006, **8**, 363.

8 (*a*) B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3943. (*b*) G. Berthon-Gelloz and T. Hayashi, *J. Org. Chem.*, 2006, **71**, 8957.

9 C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson and M. G. Organ, *Chem. –Eur. J.*, 2006, **12**, 4743.

10 M. Enders, G. Kohl and H. Pritzkow, *J. Organomet. Chem.*, 2001, **622**, 66.

11 Crystal data for Rh((*S*,*S*)-**1f**)[(η^6-C_6H_5)BPh_3] (CCDC734763) are reported in Electronic Supplementary Information (CIF).

12 For reviews, see: (*a*) M. Hatano, T. Miyamoto and K. Ishihara, *Curr. Org. Chem.*, 2007, **11**, 127. (*b*) F. Schmidt, R. T. Stemmler, J. Rudolph and C. Bolm, *Chem. Soc. Rev.*, 2006, **35**, 454. (*c*) L. Pu and H.-B. Yu, *Chem. Rev.*, 2001, **101**, 757. (*d*) K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833. (*e*) R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49.

13 For selected examples of asymmetric addition of diphenylzinc to aldehydes, see: (*a*) P. I. Dosa, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1997, **62**, 444. (*b*) C. Bolm and K. Muñiz, *Chem. Commun.*, 1999, 1295. (*c*) W.-S. Huang and L. Pu, *J. Org. Chem.*, 1999, **64**, 4222. For selected examples of asymmetric addition of diarylzinc generated from arylboron reagents, see (*d*) C. Bolm and J. Rudolph, *J. Am. Chem. Soc.*, 2002, **124**, 14850. (*e*) S. Dahmen and M. Lormann, *Org. Lett.*, 2005, **7**, 4597. (*f*) J.-X. Ji, J. Wu, T. T.-L. Au-Yeung, C.-W. Yip, R. K. Haynes and A. S. C. Chan, *J. Org. Chem.*, 2005, **70**, 1093. (*g*) X. Y. Liu, X. Y. Wu, Z. Chai, Y. Y. Wu, G. Zhao and S. Z. Zhu, *J. Org. Chem.*, 2005, **70**, 7432. (*h*) A. L. Braga, D. S. Lüdtke, F. Vargas and M. W. Paixão, *Chem. Commun.*, 2005, 2512. (*i*) M.-J. Jin, S. M. Sarkar, D.-H. Lee and H. Qiu, *Org. Lett.*, 2008, **10**, 1235.

14 Enantioselectivity up to 87% (ref. 14e) has been reported. (*a*) M. Sakai, M. Ueda and N. Miyaura, *Angew. Chem., Int. Ed.*, 1998, **37**, 3279. (*b*) T. Focken, J. Rudolph and C. Bolm, *Synthesis*, 2005, 429. (*c*) W. Zhang, Y. Qin, S. Zhang and M. Luo, *ARKIVOC*, 2005, **14**, 39. (*d*) R. B. C. Jagt, P. Y. Toullec, J. G. de Vries, B. L. Feringa and A. J. Minnaard, *Org. Biomol. Chem.*, 2006, **4**, 773. (*e*) H.-F. Duan, J.-H. Xie, W.-J. Shi, Q. Zhang and Q.-L. Zhou, *Org. Lett.*, 2006, **8**, 1479. (*f*) T. Arao, K. Sato, K. Kondo and T. Aoyama, *Chem. Pharm. Bull.*, 2006, **54**, 1576. (*g*) K. Suzuki, K. Kondo and T. Aoyama, *Synthesis*, 2006, 1360. (*h*) K. Suzuki, S. Ishii, K. Kondo and T. Aoyama, *Synlett*, 2006, 648. (*i*) T. Arao, K. Suzuki, K. Kondo and T. Aoyama, *Synthesis*, 2006, 3809.

15 (*a*) T. Arao, K. Kondo and T. Aoyama, *Tetrahedron Lett.*, 2007, **48**, 4115. (*b*) K. Yamamoto, K. Tsurumi, F. Sakurai, K. Kondo and T. Aoyama, *Synthesis*, 2008, 3585.

16 Highly enantioselective ruthenium-catalyzed arylation has been reported very recently. K. Kurihara, Y. Yamamoto and N. Miyaura, *Angew. Chem., Int. Ed.*, 2009, **351**, 4414.

17 K. Soai, Y. Inoue, T. Takahashi and T. Shibata, *Tetrahedron*, 1996, **52**, 13355.